Patients with X-linked hypophosphatemia have mutations in the PHEX gene (1), which lead to elevated intact fibroblast growth factor 23 (FGF23) levels (2). FGF23 is a hormonal factor (3) made in the bone that plays a central role in the regulation of phosphate homeostasis. Intact Fgf23 protein is cleaved by proprotein convertases (PCSKs) (4) into inactive FGF23 fragments. Our previous study using Phex mutant mice, an animal model of X-linked hypophosphatemia, revealed that these mice have markedly high intact Fgf23, but less Fgf23 fragments than in wild type mice. This observation suggested that the increased intact FGF23 in Phex mutant mice may be in part due to reduced cleavage of intact Fgf23 protein. Therefore, we hypothesized that the reduction of Pcsk expression or increased expression of Pcsk inhibitors leads to the reduced cleavage of Fgf23 protein and thus, the higher intact FGF23 in Phex mutant mice. To test this hypothesis, we synthesized cDNA from total RNA extracted from femurs of Phex mutant mice and their normal littermates and measured the expression of seven proprotein convertases (Pcsk1, Pcsk2, Pcsk3, Pcsk4, Pcsk5, Pcsk6, and Pcsk7) and one endogenous proprotein convertases inhibitor (Scg5). Our analysis of these genes showed that there was no significant difference in expression of Pcsk’s and Scg5 between Phex mutant mice and normal mice, indicating that expression of these genes does not explain the reduced proteolytic cleavage of intact Fgf23 in Phex mutant mice. Instead, our data suggests that changes in the enzymatic activity of proprotein convertases may be responsible increased proportion of intact Fgf23 in Phex mutant mice.

References


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